EVALUATION OF EFFICACY OF LASER FIBROTOMY AND INTRALESIONAL STEROID INJECTIONS WITH HYALURONIDASE IN THE TREATMENT OF ORAL SUBMUCOUS FIBROSIS – A RANDOMIZED CLINICAL TRIAL.

A SYNOPSIS

Submitted for the Registration for the Degree

of

Doctor of Philosophy

in

ORAL MEDICINE & RADIOLOGY

Faculty of Dental Science

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(Year 2024)

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Abstract of the Research Proposal

Oral submucous fibrosis (OSMF) is an insidious disease primarily connected with fibroelastic alterations in the oral mucous membrane, resulting in a sensation of burning and a gradual decrease in mouth opening. The management of OSMF relies on empirical approaches, contingent on the condition's staging, and encompasses a combination of conservative, medical, and surgical interventions. Handling moderate OSMF poses increased challenges due to the limited effectiveness of conservative and medical treatments, coupled with the prolonged duration of medical care that escalates expenses. Additionally, issues such as patient non-compliance arise, and the potential for adverse systemic effects accompanies surgical techniques like fibrotomy and the subsequent reconstruction of defects, particularly when performed under general anesthesia (GA). This approach also introduces the added risk of managing a difficult airway, in addition to the typical risks associated with GA. One of the latest revolutions in the field of medicine and dentistry has been the advent of lasers. An alternative method to perform surgical fibrotomy in moderate OSMF cases is the use of lasers. The benefits provided by lasers are that they can be used with local anesthesia and are minimally invasive. The operating time is reduced, there is minimal bleeding and faster healing as well as less scarring of the surgical site, when lasers are used.

In the proposed **Single-blinded Randomized Clinical trial**, 60 patients with a clinical and histopathological diagnosis of moderate OSMF will be recruited using thorough inclusion and exclusion criteria. The patients will be randomly assigned into two treatment groups, i.e. Group A patients will be treated with Laser fibrotomy, and Group B patients will be treated with intralesional injections of Dexamethasone and Hyaluronidase.

In Group A, Diode laser fibrotomy will be performed under local anesthesia using a Diode laser (980 nm frequency) at 2 W power in contact mode with a fiber-optic cutting tip. In Group B, patients will undergo bi-weekly intralesional injections of Dexamethasone and Hyaluronidase. Both groups will be advised to actively participate in mouth-opening exercises. The assessment of improvements in mouth opening and cheek flexibility, as well as the reduction in oral cavity burning sensation, will be conducted before and after the treatment over a period of 6 months

Keywords: Oral submucous fibrosis. Diode laser. Fibrotomy, intralesional steroid injections

Introduction

Oral submucous fibrosis (OSMF) stands as a prevalent oral potentially malignant disorder (OPMD), known for its potential to lead to significant morbidity. The primary etiological factor for OSMF is the consumption of areca nut, with other contributing elements including smokeless tobacco, chili consumption, nutritional factors, genetics, autoimmunity, and infections.[1-3] Oral submucous fibrosis is a chronic inflammatory disorder with juxta-epithelial hyalinization. It further leads to fibrosis of the lamina propria and fibrous bands formation in the connective tissue. The clinical features of OSMF are a burning sensation in the oral cavity to spicy food and, a gradual decrease in the mouth opening which leads to difficulty in mouth opening, chewing, and swallowing of food. This compromises the quality of life for the patients.[4] In advanced stages, fibrous bands deposit in the buccal mucosa and other sites, resulting in increased trismus, speech, and deglutition defects, a shrunken uvula, and culminating in premalignant and malignant changes in the oral mucosa. The prevalence of OSMF is notably higher in the Southeast Asia region due to the prevalent habit of areca nut (AN) chewing.[5-7] According to the World Health Organization (WHO), over 5 million people globally are affected by OSMF, cutting across various age groups.[8] The prevalence rate of OSMF in India is approximately 0.2%–0.5%, a surge attributed to the increased use of commercially prepared areca nut and tobacco products. OSMF is a potentially pre-malignant condition of the oral cavity with transformation into malignancy reported at as high as 7.6% globally. Clinically, OSMF is classified into four groups based on the severity of trismus and the extent of fibrosis of oral mucosa (Table 1).[11-14] Oral submucous fibrosis (OSMF) is primarily addressed with a key focus on improving mouth opening as a major clinical outcome. The management of OSMF encompasses a blend of conservative/medical and surgical interventions[15,16]. In the early and mild stages, conservative approaches involve quitting tobacco chewing, oral exercises, systemic antioxidants, nutritional supplements, and diet counseling. Topical corticosteroids play a pivotal role in managing mild cases. Moderate cases (Group II & III) often see success with a combination of conservative and medical treatments, including intralesional injections of steroids and collagenases like hyaluronidase.[17-38] Other options include placentrex injections, systemic corticosteroids, immunomodulators, and pentoxyfilline.[39-55] Biweekly intralesional steroid injections, with or without hyaluronidase, are considered highly effective. However, the benefits diminish in moderate and advanced stages, necessitating prolonged treatment with modest outcomes and potential relapses. Extended medical treatment raises costs, poses challenges with patient compliance, and increases the risk of adverse systemic effects. Surgical methods are employed in OSMF cases with severe trismus, utilizing conventional techniques fraught with challenges like heightened intraoperative bleeding and secondary healing leading to further fibrosis.[11-14] Electrosurgical techniques may reduce bleeding but

pose risks of deep tissue damage. Radical surgical interventions are reserved for cases requiring substantial mouth opening, involving excision of fibrotic bands and subsequent reconstruction.[56-69] Managing moderate OSMF (Groups II and III) presents challenges as conservative and medical approaches show limited efficacy, and aggressive surgery is often not justified. To address the drawbacks of conventional surgical fibrotomy, lasers present an alternative with advantages such as minimal bleeding, use with local anesthesia, minimal invasiveness, and reduced postoperative fibrosis.[70-87] Various laser types, including Diode, KTP-532, and Er, Cr: YSGG, have been utilized for fibrotomy in moderate and advanced OSMF cases. Diode lasers, in particular, offer portability, cost-effectiveness, and enhanced patient compliance.[71-79]

Despite these advancements, there is a lack of studies comparing the efficacy of laser fibrotomy with intralesional steroid injections in moderate-stage OSMF. This study aims to fill this gap by exploring and comparing the effectiveness of laser fibrotomy and conventional intralesional steroid injections in managing moderate-stage OSMF patients.

Review of Literature

1. **Gupta S et al (2018)** conducted a study on patients with moderate OSMF to assess the effectiveness of diode laser fibrotomy. Additionally, the study aimed to establish correlations between habit variables and the occurrence of OSMF. The study included thirty patients who were clinically and histopathologically diagnosed with moderate-stage OSMF. Laser fibrotomy procedures were performed on these patients under local anesthesia, utilizing a Zolar diode laser (980 nm frequency) with a 2-W power setting in contact mode, employing a fibro-optic cutting tip. Patients were instructed to practice mouth-opening exercises rigorously, and a topical corticosteroid was administered for burning sensation and pain management over 6 months. The study conducted pre- and post-treatment comparisons, analyzing variables such as improvement in mouth opening, reduction in burning sensation, improvement in tongue protrusion, and cheek flexibility after a follow-up period of 9 months post-surgery. Following the 9-month follow-up period, the statistical analysis revealed a significant mean difference in pre- and post-treatment values of the Visual Analog Scale (VAS) score, mouth opening, and tongue protrusion. The study's conclusion indicated that lasers present an alternative and superior approach to surgical fibrotomy in relieving trismus associated with moderate OSMF. This is attributed to their minimally invasive nature, causing less hemorrhage, facilitating faster healing, and resulting in minimal surgical site scarring and relapse.

2. In their study, **Chaudhry Z et al (2014)** investigated the efficacy of Erbium Chromium Yttrium Scandium Gallium Garnet (ErCr: YSGG) laser fibrotomy in treating 16 cases of moderate oral submucous fibrosis (OSMF). The procedure was performed under local anesthesia, coupled with the implementation of habit cessation, topical steroids, lycopene, and oral physiotherapy. The study revealed a significant improvement in mouth opening from the preoperative to the 1-year postoperative period. Moreover, the mean difference in Visual Analog Scale scores for oral burning sensation, was also statistically significant, indicating improvement. The conclusion drawn from the study was that ErCr: YSGG laser fibrotomy, performed under local anesthesia, represents a minimally invasive, cost-effective, chairside procedure that serves as a valuable adjunct in the management of moderate OSMF.

3. In their systematic review, **Gupta S and Jawanda MN (2021)** explored the role of lasers as a promising non-invasive technique for treating oral submucous fibrosis (OSMF). Their conclusion highlighted that in premalignant conditions like OSMF, lasers offer a reliable and reproducible method, effectively preventing further morbidity. The advantages include a bloodless surgical field, minimal operating time, and the least patient discomfort, leading to effective long-term postoperative results for both the surgeon and the patient. The review further emphasized that there is limited research on the use of lasers in OSMF treatment, and the existing studies primarily focus on specific lasers. Therefore, the authors recommended the need for large-scale studies to investigate the higher efficacy and potential unknown effects of other lasers utilizing this technology.

4. In their randomized controlled trial (RCT) study, **Talsania JR et al (2016)** investigated the use of a diode laser fibrotomy in eight patients with OSMF having trismus, conducted between 2002 and 2006. The study concluded that the diode laser yielded favorable results for all patients. It was suggested that the diode laser serves as a cost-effective and alternative method, particularly in Group III and Group IVA cases, where bilateral temporalis myotomy and coronoidectomy are often considered the only viable solution. The technique involving the diode laser was highlighted for its reduced morbidity, making it a suitable choice for the Asian population. Additionally, it requires less hospital stay and follow-up compared to other surgical methods, further contributing to its feasibility and effectiveness.

5. In their comprehensive systematic review of the treatment outcomes of laser therapy in oral submucous fibrosis (OSMF), **Gondivkar SM et al (2020)** reached the conclusion that lasers offer a promising and improved approach for alleviating trismus and potentially addressing other symptoms associated with moderate stages of the disease. The advantages of lasers include their minimal invasiveness, good tolerability, time and cost-effectiveness, sustainable outcomes, and reduced morbidity.

6. In their study, **Nayak DR et al (2008)** investigated the use of a KTP-532 laser for the release procedure in nine cases of moderate to advanced stage OSMF within the ENT–head and neck surgery department of a tertiary center. The study observed a significant difference in the mouth opening of the patients before and after treatment. This preliminary research suggested that the KTP-532 laser release procedure can effectively

achieve significant improvement in mouth opening in OSMF cases with minimal morbidity and satisfactory results.

7. **Tilakaratne WM et al (2016)** have conducted a study on 230 histologically confirmed patients with OSMF using intralesional corticosteroids as a treatment for restricted mouth opening. They observed that there was a statistically significant difference in the ability to open the mouth over 12 months in the patients who had corticosteroid injections and concluded that intralesional corticosteroid injection is one of the most widely implemented interventions for OSMF at present, particularly for those patients with palpable fibrous bands.

8. In their, **James L et al (2015)** conducted a randomized controlled trial (RCT) on the management of Grade III Oral Submucous Fibrosis (OSMF) and administered biweekly intralesional injections of Hyaluronidase and Dexamethasone over 4 weeks to a total of 28 patients, monitoring them for 9 months. The study concluded that this approach is an effective method for managing Grade III OSMF. It was suggested that this non-surgical intervention could potentially eliminate the associated morbidity linked with surgical management. Additionally, the study highlighted the cost-effectiveness of this method as a management strategy.

9. **Joshna Ek et al (2023)** in a non-randomized prospective study conducted on patients with clinical stage II OSMF treated with weekly intralesional injection of placentrex and hyaluronidase + dexamethasone respectively, for six weeks concluded that both intralesional placentrex and hyaluronidase + dexamethasone injection are effective in reducing the symptoms of stage II OSMF. However, hyaluronidase + dexamethasone injection showed slightly better results in terms of improvement in mouth opening and reduction in burning sensation after six weeks.

10. **Yadav A et al (2020)** conducted a prospective clinical trial evaluating the efficacy of intralesional injection of Triamcinolone acetonide (40mg/ml) and hyaluronidase (1500IU) with regular oral physiotherapy exercises in 30 subjects of clinically diagnosed Oral submucous fibrosis. The patients were given biweekly injections (18 injections) of Triamcinolone Acetonide and hyaluronidase for a total period of 9 weeks and followed up for 16 weeks. All subjects were advised adjunctive oral physiotherapy exercises for mouth opening and cheek flexibility. Clinical improvement was evaluated by a visual analog

scale for pain/burning sensation, and interincisal mouth opening in mm. They concluded that Intralesional steroid injections with hyaluronidase biweekly along with oral physiotherapy show promising results in symptomatic relief of OSMF.

11. **Khan MK et al (2015)** conducted a prospective randomized study on 30 cases of oral sub-mucous fibrosis, for 18 months. Patients were divided into three groups of 10 each randomly and were given intraoral injections of hydrocortisone and hyaluronidase, dexamethasone and hyaluronidase, triamcinolone and hyaluronidase at weekly intervals for 12 weeks. Treatment outcome was evaluated based on improvement in symptoms, signs, and clinical improvement. They concluded that there was a statistically significant improvement in burning sensation, relief from ulceration and vesiculation, good improvement in mouth opening, and a decrease in fibrous bands in all three groups.

12. **Kisave P et al (2020)** conducted a study to evaluate the efficacy of injection of placentrex and injection hydrocortisone in OSMF patients in increasing mouth opening and reducing the burning sensation. They recruited 60 patients with Stage II and Stage III OSMF, who were randomly divided into two groups and were administered submucosal injections of hydrocortisone and placentrex along with physiotherapy and oral iron, nutrients, and B-carotene supplements for 2 months. They concluded that statistically significant difference in reduction in burning sensation, improvement in the mouth opening, and improvement in mucosal health was noted to be better in patients who were given submucosal injections of hydrocortisone than in patients who were given submucosal injections of placentrex.

13. **Goldar GK et al (2023)** conducted a study in the Department of Otorhinolaryngology & Head Neck Surgery, with a total sample of 80 OSMF patients divided into two groups, group A received Inj. Triamcinolone acetonide and group B received Inj. Triamcinolone Acetonide and Hyaluronidase 1500 IU at weekly intervals. Pre-treatment and post-treatment clinical and histopathological profiles of the patients were recorded and analyzed. The group that received injections of Triamcinolone acetonide and Inj. Hyaluronidase showed a better improvement on post-treatment histopathological grading and both groups showed statistically significant improvement in the clinical parameters.

14. **Mehta D et al (2021)** conducted a prospective randomized study including 10 patients who were treated surgically for OSMF. Patients with the chief complaint of long-standing difficulty in mouth opening (less than 20mm) were recruited for the study. This

prospective study was carried out to evaluate the use of the Naso-labial flap as a grafting technique in OSMF cases and observe the surgical outcome in terms of post-surgical mouth opening. All the patients showed sustained mouth opening, satisfactory epithelialization, and minimum wound contracture. They concluded that the Naso-labial flap has proven to be a useful and reliable treatment modality.

15. In their study, **Chang YM et al (2004)** investigated the treatment of trismus in thirty patients with betel nut chewing-induced oral submucous fibrosis. The patients were divided into two groups: group I, treated with fibrotic tissue release only, and group II, treated with fibrotic tissue release along with masticatory muscle myotomy and coronoidotomy. The additional procedures in group II were specifically performed for patients with an intraoperative interincisal distance remaining less than 35 mm immediately after submucous fibrous tissue release. The study concluded that submucous fibrotic tissue release is an effective procedure for treating trismus resulting from betel nut chewing-induced submucous fibrosis. Furthermore, the addition of masticatory muscle myotomy and coronoidotomy was deemed useful, particularly in the treatment of severe forms of the condition.

Research Hypothesis

Null Hypothesis

There is no statistically significant difference in the clinical outcome parameters in terms of improvement in mouth opening, reduction in burning sensation, and improvement in cheek flexibility in the laser fibrotomy treatment group when compared with the intralesional treatment group.

Alternate Hypothesis

There is a significant difference in the clinical outcome parameters in terms of improvement in mouth opening, reduction in burning sensation, and improvement in cheek flexibility in the laser fibrotomy treatment group when compared with the intralesional treatment group.

Research Aim and Objectives

Aim

The proposed study seeks to conduct a clinical comparison and assessment of the effectiveness between Diode laser fibrotomy and Intralesional Dexamethasone sodium phosphate steroid injections with Hyaluronidase in the management of moderate (Group II & III) Oral Submucous Fibrosis (OSMF) patients.

Objectives

1. To assess the clinical outcome parameters from baseline to 6 months post-treatment using laser fibrotomy and intralesional dexamethasone sodium phosphate steroid injections with hyaluronidase in moderate Oral Submucous Fibrosis (OSMF) patients.

2. To assess patient's oral burning sensation from baseline to 6 months post-treatment using Visual Analog Score (VAS) in moderate OSMF patients treated with laser fibrotomy and intralesional dexamethasone sodium phosphate steroid injections with hyaluronidase.

3. To compare the clinical efficacy of laser fibrotomy and intralesional dexamethasone sodium phosphate steroid injections with hyaluronidase in moderate OSMF patients.

Material and Methods

Sample Selection

The proposed study will adopt a randomized controlled, parallel-arm design. The study protocol will undergo submission to the institutional ethics committee at Sri Sai College of Dental Surgery, Vikarabad, Telangana, seeking approval. The participant pool will consist of 60 systemically healthy individuals diagnosed with Oral Submucous Fibrosis (OSMF), aged between 18 to 65 years. Recruitment will be conducted from the Outpatient Department of Oral Medicine and Radiology at Sri Sai College of Dental Surgery, Vikarabad, adhering to specific inclusion and exclusion criteria.

Inclusion criteria

1. Patients exhibiting the clinical characteristics aligned with group II and group III Oral Submucous Fibrosis (OSMF), as per Khanna and Andrade's clinical classification.
2. A minimum mouth opening of 1.5 cm or more is required for eligibility.

Exclusion criteria

1. Patients expressing unwillingness to participate in the study.
2. Individuals with cardiac, respiratory, renal, and hepatic diseases are excluded.
3. Patients exhibiting drug allergies are not eligible for inclusion.
4. Those who have undergone prior treatments for Oral Submucous Fibrosis (OSMF) are also excluded.

- A detailed case history including habit history will be recorded for each patient (Annexure I), and informed consent for participation in the study will be taken before the recruitment into the study. (Annexure-II)

Randomization of the Study

The selected patients will be randomly assigned using computer-generated randomization into two groups.

Group A – Laser fibrotomy using diode laser

Group B – Intralesional steroid injections of dexamethasone sodium phosphate with hyaluronidase

Materials

1. Diagnostic instruments- Mouth mirror, Straight probe & Vernier Callipers.
2. A 980-nm solid-state diode laser for oral soft tissues (Model— Pioon 980 nm,10 watts, Pioon Technology Co. Ltd, Wuhan, Hubei, China)
3. Dexamethasone Sodium Phosphate Injection, 4 mg / mL, 2 mL Single-Dose Vial
4. Hyaluronidase 1500 I.U. Powder for Solution for Injection/Infusion
5. Local anesthetic with 2% w/v lignocaine and adrenaline in the ratio of 1:80,000.
6. Topical Triamcinolone acetonide gel 0.1 %
7. Cap. Lycopene 4 mg
8. Thread and marker pen

Methodology

Clinical examination

All the subjects included in this study will undergo a complete clinical evaluation at the pre-baseline visit (Annexure I). The clinical parameters i.e., mouth opening, burning sensation, and cheek flexibility will be recorded at baseline and 1 month, 3 months, and 6 months follow-up.

Clinical parameters:- The following clinical parameters will be recorded:

1. Mouth opening (MO): The measurement of mouth opening will be conducted using vernier calipers, determining the distance between the mesioincisal edge of the upper left central and the mesioincisal edge of the lower left central incisor tooth in millimeters. The assessments will include baseline measurement (MOb), measurements at 1 month (MO1), 3 months (MO3), and 6 months (MO6) during the study.

2. Burning sensation (BS): The evaluation of the burning sensation was conducted through the Visual Analog Scale (VAS), a line graded from 0 (indicating no burning sensation) to 10 (representing the strongest burning sensation). Patients were required to self-assess their symptoms and quantify the intensity by marking a corresponding number on the scale. The assessments included burning sensation at baseline (BSb), at 1 month (BS1), at 3 months (BS3), and 6 months (BS6).

3. Cheek flexibility (CF): Cheek flexibility was assessed by measuring two points, each located one-third of the distance from the angle of the mouth on a line connecting the tragus of the ear and the angle of the mouth (v1). The subject was instructed to fully inflate their cheeks, and the distance between the two points marked on the cheek was measured (v2). Cheek flexibility was calculated as the difference between v2 and v1 (Cheek flexibility at baseline: CFb, at 1 month: CF1, at 3 months: CF3, at 6 months: CF6).

Clinical outcome parameters: the clinical outcome parameters i.e. improvement in mouth opening (in millimeters), reduction in burning sensation (using Visual Analogue Scale (VAS), improvement in cheek flexibility (in millimeters)- will be assessed at 1 month, 3 months, and 6 months post-treatment follow-up.

Improvement in mouth opening (iMO):

At 1-month post-treatment: $iMO_1 = MO_1 - MO_b$

At 3 months post-treatment: $iMO_3 = MO_3 - MO_1$

At 6 months post-treatment: $iMO_6 = MO_6 - MO_3$

Reduction in burning sensation (rBS):

At 1-month post-treatment: $rBS_1 = BS_1 – BS_b$

At 3 months post-treatment: $rBS_3 = BS_3 – BS_1$

At 6 months post-treatment: $rBS_6 = BS_6 – BS_3$

Improvement in cheek flexibility (iCF):

At 1-month post-treatment: $iCF_1 = CF_1 – CF_b$

At 3 months post-treatment: $iCF_3 = CF_3 – CF_1$

At 6 months post-treatment: $iCF_6 = CF_6 – CF_3$

Study design:

The proposed study will include a total of 5 visits for Group A, one pre-treatment, one treatment, and three post-treatment follow-up visits (1 month, 3 months, and 6 months follow-up visits) and 8 visits for Group B one pre-treatment, four treatment, and three post-treatment follow-up visits (1 month, 3 months and 6 months follow up visits).

Pre-treatment protocol (Visit 1):

- Patients diagnosed with moderate (Grade II & III) OSMF will be screened for eligibility for recruitment into the study. Written informed consent will be obtained from the patients. The selected patients will be allocated randomly to either Group A – Laser fibrotomy using diode laser or Group B – Intralesional injections of dexamethasone sodium phosphate with hyaluronidase using computer-generated randomization. Clinical parameters, including mouth opening, burning sensation, and cheek flexibility, will be meticulously documented. Patients will receive encouragement to cease oral chewing habits, and oral prophylaxis will be conducted. Additionally, comprehensive oral hygiene instructions will be provided. To eliminate potential sources of chronic intraoral trauma, such as sharp teeth, calculus, and appliances, necessary interventions will be performed for all patients before the initiation of treatment.

Treatment protocol for Group A (Visit 2):

Clinical parameters i.e., mouth opening, burning sensation, and cheek flexibility will be recorded before the treatment.

Laser fibrotomy will be conducted under local anesthesia (2% w/v lignocaine and adrenaline in a ratio of 1:80,000) using a 980-nm solid-state diode laser designed for oral soft tissues (Model- Pioon

980 nm, 10 watts, Pioon Technology Co. Ltd, Wuhan, Hubei, China). The laser will be employed per the manufacturer's manual instructions. A metal handpiece with a disposable cutting fiber of 400 µm diameter will be utilized in continuous wave emission mode at 2-W power in contact mode. The total energy calculated will be 4 J, and the fluence will be maintained at 50 J/cm2. A diode laser is used to make an inverted Y-shaped incision in the buccal mucosa, with a depth of 2 mm. This will cut through all palpable fibrotic bands. In cases where fibrotic bands are present anteriorly, the incisions will be extended anteriorly up to the commissures. Finger palpation will be employed to break the fibrous bands, and simultaneously, Heister's mouth opener will be utilized to separate the cut fibrous bands, facilitating an increase in mouth opening. Patients will be instructed to diligently practice mouth-opening exercises using a bunch of ice cream sticks five times a day. Additionally, topical corticosteroid (triamcinolone acetonide gel 0.1%) will be administered as a topical application thrice daily for 2 months post-treatment to alleviate burning sensation and pain.

Treatment protocol for Group B (Visit 2,3,4 and 5):

Clinical parameters i.e., burning sensation, mouth opening, and cheek flexibility will be recorded before the treatment.

The patients will be administered submucosal intralesional injections of 1.5ml Dexamethasone sodium phosphate (Inj Decadron 4 mg/ml) and 1500 International Units of Hyaluronidase (Hynidase 1500 I.U.) mixed with 0.5 ml of 2% (1:80,000) Lignocaine Hydrochloride once in every 2 weeks (biweekly) for 4 weeks. The selection of the sites of injection will be based on clinical judgment. Injections will be given just below the mucosa, at multiple sites with a 26-gauge needle.

Common therapy to Group A & Group B

Conservative therapy, standardized for all patients, will encompass the following components:

1. Topical application of steroids, utilizing triamcinolone acetonide gel 0.1%, administered thrice daily for 2 months.
2. Systemic Antioxidant supplementation, specifically Cap Lycopene 4 mg, administered twice daily for 2 months.
3. Oral physiotherapy, involving cheek ballooning and mouth-opening exercises utilizing a bunch of ice-cream sticks, is to be performed four times daily for 5 minutes each session, continuing for 6 months post-treatment.

Furthermore, all patients will be actively enrolled in the tobacco cessation clinic at our institute before the initiation of treatment.

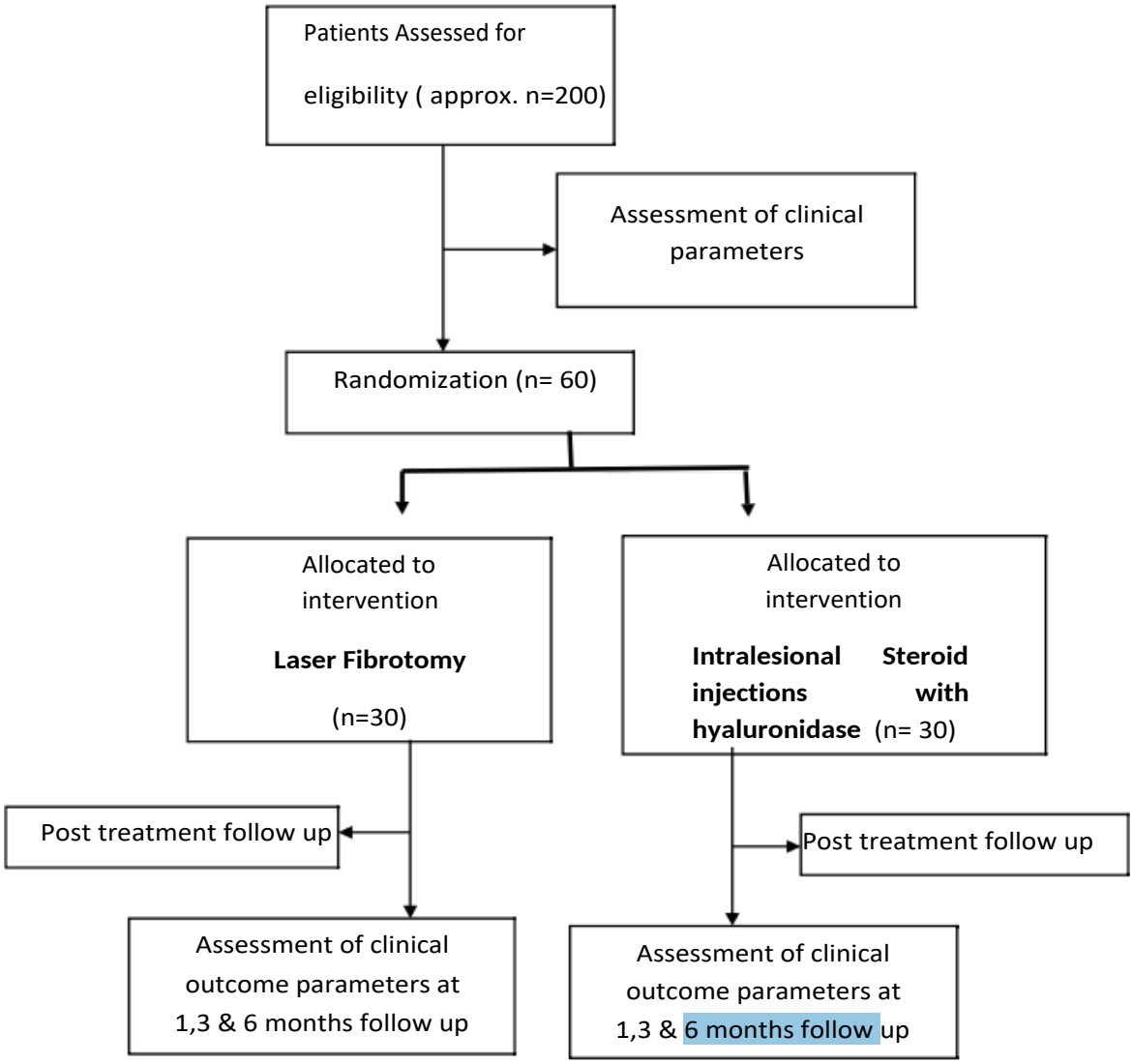
Post-Treatment Protocol:

Visit 3 for Group A& Visit 6 for Group B (1 Month follow-up visit):
The clinical outcome parameters i.e. improvement in mouth opening (in millimeters), reduction in burning sensation using Visual Analogue Scale (VAS), and improvement in cheek flexibility (in millimeters)- will be recorded. Oral physiotherapy and oral hygiene instructions will be reinforced.

Visit 4 for Group A& Visit 7 for Group B (Three months follow-up visit): The clinical outcome parameters i.e. improvement in mouth opening (in millimeters), reduction in burning sensation (using Visual Analogue Scale (VAS), improvement in cheek flexibility (in millimeters)- will be recorded. Oral physiotherapy and oral hygiene instructions will be reinforced.

Visit 5 for Group A& Visit 8 for Group B (Six-month follow-up visit): The clinical outcome parameters i.e. improvement in mouth opening (in millimeters), reduction in burning sensation using Visual Analogue Scale (VAS), improvement in cheek flexibility (in millimeters)- will be recorded. Oral physiotherapy and oral hygiene instructions will be reinforced. This will be the final appointment of a 6-month follow-up. Patients will be recalled once in 3 months for regular follow-up.

Data Flow & Biostatistics


Patients Assessed for eligibility (approx. n=200)
Assessment of clinical parameters
Randomization (n= 60)
Allocated to intervention Laser Fibrotomy (n=30)
Allocated to intervention Intralesional Steroid injections with hyaluronidase (n= 30)
Post treatment follow up
Post treatment follow up
Assessment of clinical outcome parameters at 1,3 & 6 months follow up
Assessment of clinical outcome parameters at 1,3 & 6 months follow up

Sample size calculation:

Sample size was calculated using an online sample size calculator, Clincalc.com (https://clincalc.com/stats/samplesize.aspx).

The sample size was calculated for a two-arm Randomised Controlled Trial, using the clinical outcome parameters,e; improvement in mouth opening in millimeters.

The online tool applies the following formula for calculating the sample size of each group.

The online calculator suggested a Sample size of 28 for each group, which is rounded off to 30. This upward adjustment also can take care of loss to follow up, if any.

Ref: **Rosner B. *Fundamentals of Biostatistics*. 7th ed. Boston, MA: Brooks/Cole; 2011.**

Sample Size	
Group 1	28
Group 2	28
Total	**56**

Study Parameters	
Mean, group 1	5
Mean, group 2	3.5
Alpha	0.05
Beta	0.2
Power	0.8

View Power Calculations

$$k = \frac{n_2}{n_1} = 1$$

$$n_1 = \frac{(\sigma_1^2 + \sigma_2^2/K)(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}$$

$$n_1 = \frac{(2^2 + 2^2/1)(1.96 + 0.84)^2}{1.5^2}$$

$$n_1 = 28$$

$$n_2 = K * n_1 = 28$$

$\Delta = |\mu_2 - \mu_1|$ = absolute difference between two means
σ_1, σ_2 = variance of mean #1 and #2
n_1 = sample size for group #1
n_2 = sample size for group #2
α = probability of type I error (usually 0.05)
β = probability of type II error (usually 0.2)
z = critical Z value for a given α or β
k = ratio of sample size for group #2 to group #1

Sixty patients diagnosed with moderate(group II & III) OSMF will be recruited and randomly allocated either to Group A or Group B from the Dept. of Oral Medicine and Radiology, Sri Sai College of Dental Surgery, Vikarabad, Telangana. The time to complete the study will be around one year.

The Demographic data and Clinical parameters will be recorded for each patient in case proforma prepared for the study. The clinical parameters i.e., mouth opening, burning sensation, and cheek flexibility will be recorded at baseline and 1 month, 3 months, and 6 months post-treatment follow-up. The clinical outcome parameters i.e.; improvement in mouth opening (in millimeters), reduction in burning sensation using Visual Analogue Scale (VAS), and improvement in cheek flexibility (in millimeters) will be assessed at 1 month, 3 months, and 6 months post-treatment follow-up. The collected data will be analyzed using appropriate biostatistical tests using *SPSS version 20* software.

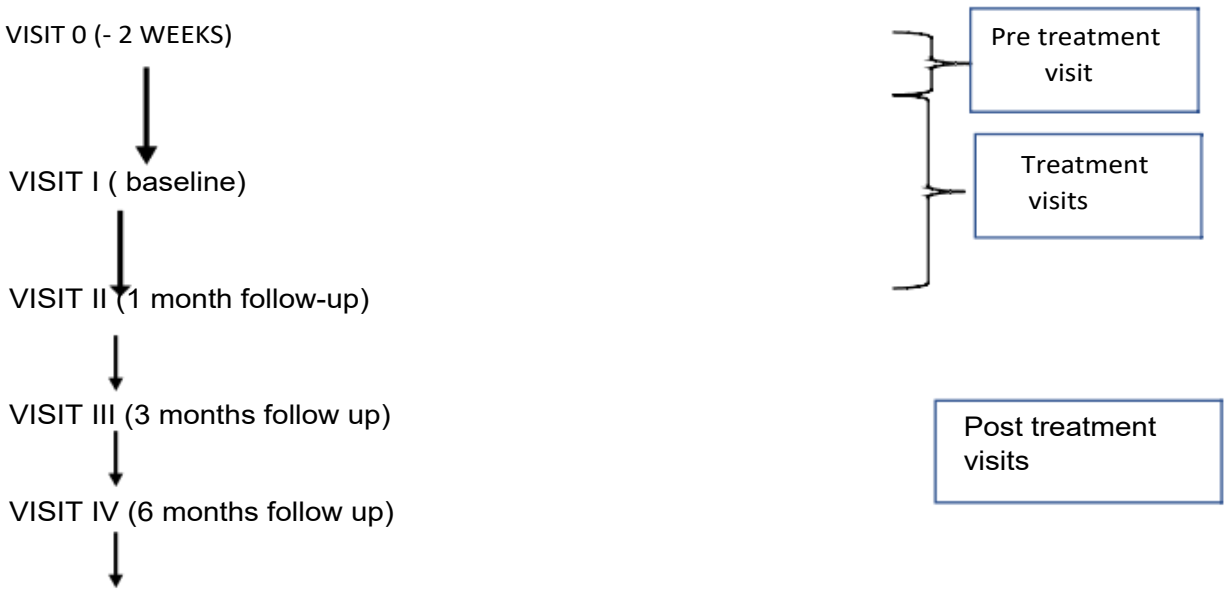
Work plan

The proposed study will be conducted in the Department of Oral Medicine and Radiology, Sri Sai College of Dental Surgery, Vikarabad, established in the year 2000. The P.G. program was started in the Department of Oral Medicine and Radiology in the year 2007. Currently, I am working as a Professor in the Department of Oral Medicine and Radiology and associated with the institute for the past 17 years.

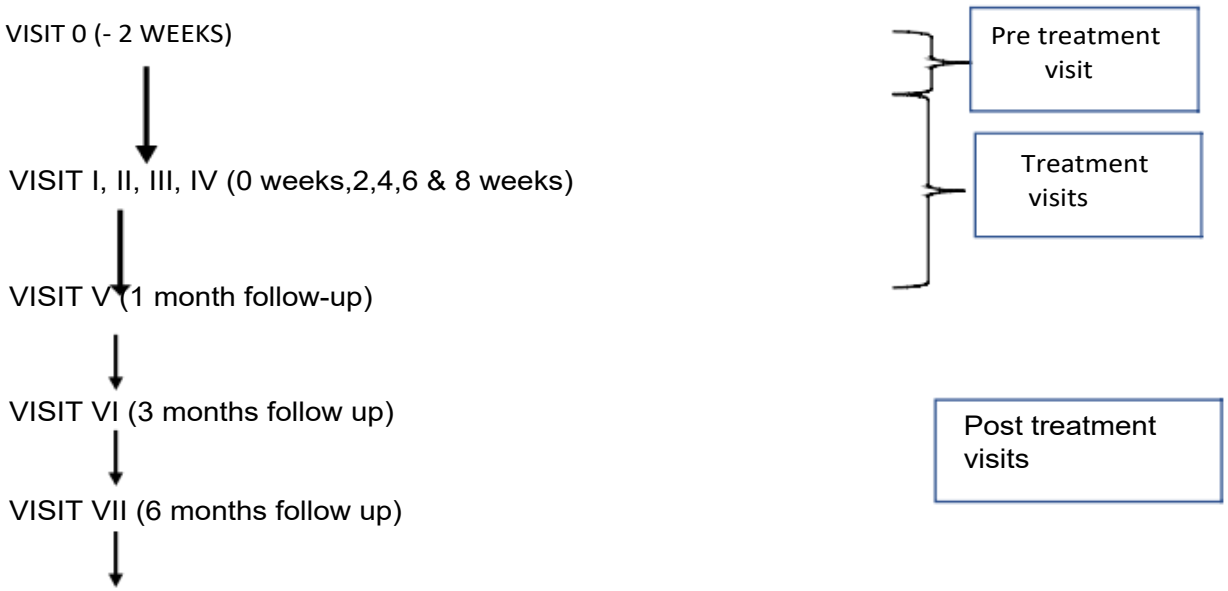
The average number of patients with OSMF attending the outpatient Department of Oral Medicine and Radiology, Sri Sai College of Dental Surgery per month is around 40. The proposed study sample size will consist of 60 patients diagnosed with moderate OSMF. The recruitment of 60 patients will be done in 2 to 4 months. The proposed study duration will be around 1 year.

In Group A, laser fibrotomy will be done in a single visit with an approximate treatment time of 30 minutes to 45 minutes. The post-treatment follow-up will be for the next 6 months (3 visits: 1 month, 3 months & 6 months post-treatment). The overall study period for Group A will be around 8 to 10 months.

In Group B, intralesional dexamethasone sodium phosphate injections with hyaluronidase will be given biweekly in 4 visits in 2 months, with approximate treatment time of 10 minutes to 20 minutes in each visit. The post-treatment follow-up will be for the next 6 months (3 visits: 1 month, 3 months & 6 months post-treatment). The overall study period for Group B will be around 10 to 12 months.


VISIT 0 (- 2 WEEKS)
VISIT I (baseline)
VISIT II (1 month follow-up)
VISIT III (3 months follow up)
VISIT IV (6 months follow up)
Pre treatment visit
Treatment visits
Post treatment visits

Work Plan for Group A


VISIT 0 (- 2 WEEKS)
VISIT I, II, III, IV (0 weeks,2,4,6 & 8 weeks)
VISIT V (1 month follow-up)
VISIT VI (3 months follow up)
VISIT VII (6 months follow up)
Pre treatment visit
Treatment visits
Post treatment visits

Work Plan for Group B

The usefulness of the study

Oral submucous fibrosis (OSMF) represents a significant premalignant condition affecting the oral mucosa and oropharynx, characterized by fibrosis and the development of fibrotic bands in the connective tissue of the oral mucosa. This gradually leads to a restriction in mouth opening. Over the last four decades, the prevalence of OSMF in India has seen a notable increase from 0.03% to 6.42%. OSMF not only results in a progressive limitation of mouth opening but also induces a burning sensation in the oral cavity, significantly impacting the quality of life for affected individuals. In cases of moderate disease, the primary focus of treatment outcomes for OSMF patients is the enhancement of mouth opening. Typically, medical management involves the administration of intralesional injections of corticosteroids with hyaluronidase, considered a highly effective approach. However, given the chronic nature of OSMF, this treatment necessitates multiple visits, leading to increased expenses, patient non-compliance, and a heightened risk of adverse systemic effects. Surgical interventions, recommended for advanced stages of the disease, are often performed under general anesthesia (GA), incurring significant costs and presenting challenges such as intra-operative bleeding, post-operative pain, and the potential for relapse due to fibrosis of the surgical wound.Currently, there is a lack of consensus on the management of group II and III OSMF, as conservative treatment provides limited benefits, and aggressive surgical techniques may not be justified in these cases. The introduction of lasers in recent years has introduced an innovative treatment approach for OSMF patients with moderate disease. Laser treatment offers several advantages, including the ability to be performed under local anesthesia, a bloodless operative field, minimal invasiveness, reduced fibrosis, scarring, and tissue shrinkage post-healing, along with immediate improvement in mouth opening.

This study aims to provide insights into the clinical efficacy of laser fibrotomy in treating moderate (Grade II & III) OSMF patients. The findings from this research are anticipated to have a significant impact on the management of OSMF patients in India.

Summary of the Research Proposal

The proposed study aimed to clinically compare and evaluate the efficacy of Diode laser fibrotomy with intralesional dexamethasone sodium phosphate steroid injections with hyaluronidase in the treatment of moderate (Group II & III) Oral Submucous Fibrosis (OSMF) patients. Sixty patients diagnosed with moderate (group II & III) OSMF will be recruited and randomly allocated either to Group A or Group B from the Dept. of Oral Medicine and Radiology, Sri Sai College of Dental Surgery Vikarabad, Telangana. The time to complete the study will be around one year. The Demographic data and Clinical parameters will be recorded for each patient in the Case- proforma prepared for the study. The clinical parameters i.e., mouth opening, burning sensation, and cheek flexibility will be recorded at baseline and 1 month, 3 months, and 6 months follow-up. The clinical outcome parameters i.e, improvement in mouth opening (in millimeters), reduction in burning sensation using Visual Analogue Scale (VAS), and improvement in cheek flexibility (in millimeters) will be assessed at 1 month, 3 months, and 6 months post-treatment follow-up. The collected data will be analyzed using appropriate biostatistical tests using *SPSS version 20* software.

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Table 1: Khanna and Andrade - Staging of Oral Submucous Fibrosis

Staging	Criteria
Group I (early):	An inter-incisal distance greater than 35 mm.
Group II (mild):	Inter incisal distance of 26–35 mm.
Group III (moderate):	Inter incisal distance of 15–25 mm. Fibrotic bands are visible at the soft palate, pterygomandibular raphe, and anterior faucial pillars.
Group IV (advanced):	
IVA	Inter-incisal distance of less than 15 mm with extensive fibrosis of mucosa all over.
IVB	Premalignant and malignant changes throughout the mucosa (histologically).

ANNEXURE I

CASE SHEET PROFORMA

Evaluation of the efficacy of laser fibrotomy and intralesional steroid injections in the treatment of Oral Submucous Fibrosis – A Randomized Clinical Trial.

Proforma

Group A/Group B

Name: O.P. No:

Age/Sex: Phone No:

Address:

Chief Complaint:-

History of Present Illness:-

Medical History:-

Dental History:-

Deleterious Habits:-

Type:

Frequency:

Duration:

Clinical Features:

Hard Tissue:

Soft Tissue:

Examination of Specific Lesion:

Provisional Diagnosis:

Investigations:

Treatment Plan:

Visits	Burning Sensation on the VAS Scale	Mouth Opening through IID in mm	Cheek flexibility in mm

ANNEXURE II

INFORMED CONSENT FORM

I miss/Mr/Mrs…….. hereby give consent to Dr. C. VANI for procedures related to the study as previously explained to me and any other procedures necessary or advisable to complete the study. I have completely understood the purpose and possible complications and agree to participate on free will. I am also informed that I have every right to withdraw from the study at any instance, whatever the reason may be.

Signature of the patient

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Submission Information

Author Name	Dr. C. Vani
Title	EVALUATION OF EFFICACY OF LASER FIBROTOMY AND INTRALESIONAL STEROID INJECTIONS WITH HYALURONIDASE IN THE TREATMENT OF ORAL SUBMUCOUS FIBROSIS – A RANDOMIZED CLINICAL TRIAL
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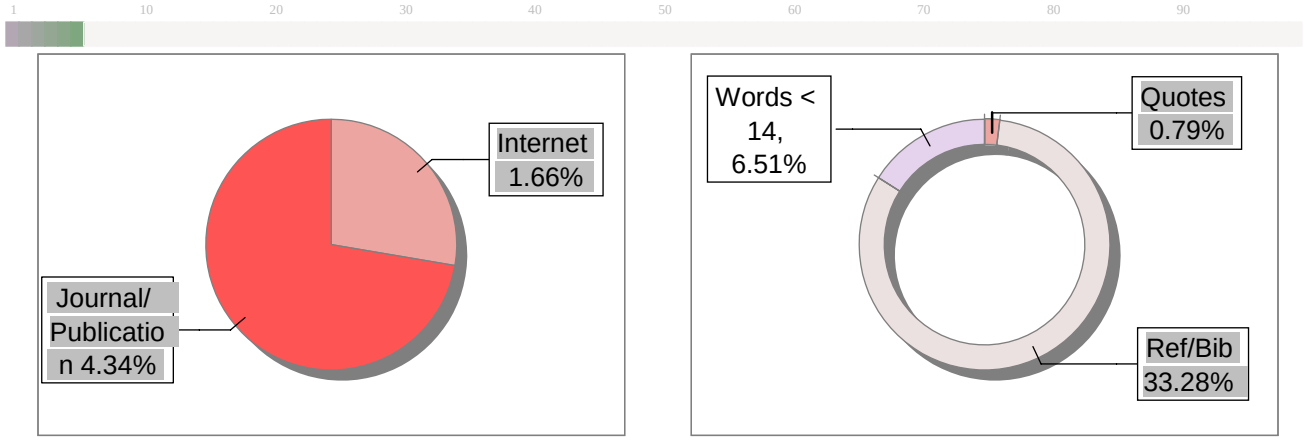

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12	journals.lww.com	<1	Internet Data
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15	Thesis submitted to shodhganga - shodhganga.inflibnet.ac.in	1	Publication
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21	actascientific.com	<1	Publication
27	www.ncbi.nlm.nih.gov	<1	Internet Data
28	Causal inference and directed acyclic graph An epidemiological concept much nee by Rao-2020	<1	Publication
30	Thesis Submitted to Shodhganga Repository	<1	Publication
33	Establishing Soft Tissue Profile Norms For Lingayat College Going Students Of Bel By Kachroo, Yasir M 2006- RGUHS	<1	Publication